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| EXAMINER | |
|---|---|
| SAIDHA, TEKCHAND | |
| **ART UNIT** | **PAPER NUMBER** |
| 1652 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/566,224 | FUJII ET AL. | |
| | Examiner | Art Unit | |
| | Tekchand Saidha | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *13-21,27-49 and 51-53* is/are withdrawn from consideration.

5)☒ Claim(s) *50* is/are allowed.

6)☒ Claim(s) *1-12 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's election of Group I (claims 1-27 & 50, elected amino acid sequence of SEQ ID NO: 2 and motif sequence 1 (SEQ ID NO: 25)) *without* traverse in the reply filed on 8/24/2010 is acknowledged.

2. Applicants state that claims 1-12, 22-26 & 50 read on the elected invention.

3. Accordingly claims 1-12, 22-26 & 50 are under consideration in this Office Action.

4. **Claims withdrawn**:

Claims 13-21, 27-49 & 51-53 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. ***Priority***

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 9.4.2003. It is noted, however, that applicant has not filed a certified copy of the priority application as required by 35 U.S.C. 119(b).

6. ***Drawings***

The drawings filed on 1/27/2006 are acknowledged.

7. ***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

8. ***Sequence Rules***

The instant specification – drawings Fig. 1A and Fig. 1B present amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), but fails to comply with the requirements. Similarly, the motif sequence 1-3 presented in the claims and/or specification (See page 8, lines 5-6, 11 & 13, for example) must be identified by sequence identifier (or SEQ ID NO:?). See also specification pages 13, 67, 68 and 69 for lack of sequence compliance. According to 37 CFR 1.821-825, every disclosed amino acid sequence of four or more residues or 10 or more nucleotides must be identified by a SEQ ID NO. Brief description of drawings for Fig. 1A and Fig. 1B may be amended to include the SEQ ID Nos. The amino acid sequence (or nucleic acid

sequence) presented requires having a sequence identifier. In order to comply with the sequence rules Applicants must identify the sequence by providing SEQ ID NO:, and where required provide a new version of the sequence listing and disk.

Applicant must submit a CRF copy and paper copy of the Sequence Listing, a statement that the content of the paper and computer readable copies are the same and where applicable include no new matter as required by 37 C.F.R. j 1.821(e) or 1.821(9 or 1.821(g) or 1 .825(d), as well as an amendment directing its entry into the specification.

Note: If the primer nucleotide sequence is already part of the sequence listing and the CRF, Applicants may amend the specification by providing the appropriate SEQ ID NO:, following the sequence.

Applicant's cooperation is requested in correcting other unidentified sequences of which applicant may become aware of in the specification.

9. ***Claim Objections***

Claims 1-12, 22-26 are objected to because of the following informalities: These claims depend upon or recite non-elected subject matter which must be deleted. Appropriate correction is required.

10. ***Claim Rejections - 35 USC § 112*** (second paragraph)

Claims 1-12, 22-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 6-8 recite the phrase 'is derived from'. The claims are vague because no derivatives of the sucrose phosphorylase sequence are disclosed. Amending the claims to recite "is obtained from", is suggested to overcome this rejection.

(b) Claim 1 is indefinite for reciting motif sequence 1 without the actual sequence identifier. Identifying the motif sequence 1 and including at the end of the sequence (SEQ ID NO: 25), is suggested to over this rejection. Claims 2-12, 22-26 are included in the rejection for failing to correct the defect present in the base claim(s).

11. ***35 U.S.C. § 112, first paragraph (Written Description)***

Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 2-3 are directed to a sucrose phosphorylase having improved thermostability according to claim 1, wherein the amino acid sequence of the natural sucrose phosphorylase has at least 40% or 60% identity with the amino acid sequence of SEQ ID NO: 2, the claimed genus.

The specification, however, only provides description of a single species of sucrose phosphorylase (SEQ ID NO: 2, from *Streptococcus mutans*) and 8 mutants thereof (see claim 50 for example). Additional modifications of the sequence motif 1 (SEQ ID NO: 25) at positions 14, 29 & 44 are also disclosed. The specification does not contain any disclosure or description of the structure and function of all amino acid sequences that are at least 40% or 60% identical to SEQ ID NO: 2, or mutants obtained from such a sequence by insertion, deletion or substitution, and which has the biological activity of a sucrose phosphorylase. The 8 species disclosed from *Streptococcus mutans* are not representative of the genus claimed. According to MPEP 2163, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v.Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed.Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.

The scope of each genus includes many members of sucrose phosphorylase enzymes with widely differing structural, chemical, and physical characteristics. Furthermore, each genus is highly variable because a significant number of structural differences between genus members exit. The specification does not describe and define any structural features and amino acid sequences commonly possessed by each genus. There is no art-recognized correlation between any structure of a sucrose phosphorylase and sequences having varying sequence homology, i.e., 40% or 60% of

SEQ ID NO: 2". Those of ordinary skill in the art would not be able to identify without further testing what specific sequences that would have sucrose phosphorylase activity. The genus of polypeptides (at least 40% or 60% of SEQ ID NO: 2) that comprise these polypeptide molecules proteins may be obtained with the aid of a computer by a skilled artisan. However, there is no teaching regarding which 40-60% of the sequence that can be varied and still result in a protein having sucrose phosphorylase activity. An important consideration is that structure is nor necessarily a reliable indicator of function. The instant specification provides no disclosure relating similarity or identity of structure to conservation of function. General knowledge in the art provides guidance to modification of some amino acids that are tolerated without losing a protein's tertiary structure.

The claim includes a genus that can be analyzed at several levels sequentially for the purpose of focusing the issue. With the aid of a computer, one of skill in the art could identify all of the amino acid sequences with at least 40% or 60% sequence identity with SEQ ID NO: 2. However, there is no teaching regarding which 40-60% of the amino acids can vary from SEQ ID NO: 2 and still result in a protein that retains sucrose phosphorylase activity. Further, there is no disclosed or art-recognized correlation between structures other than SEQ ID NO: 2 and sucrose phosphorylase activity. An important consideration is that structure is not necessarily a reliable indicator of function. In this example, there is no disclosure relating similarity of structure to conservation of function. General knowledge in the art included the knowledge that some amino acid variations are tolerated without losing a protein's tertiary structure. The results of amino acid substitutions have been studied so extensively that amino acids are grouped in so-called "exchange groups" of similar properties because substituting within the exchange group is expected to conserve the overall structure. For example, the expectation from replacing leucine with isoleucine would be that the protein would likely retain its tertiary structure. On the other hand, when non-exchange group members are substituted, e.g., proline for tryptophan, the expectation would be that the substitution would not likely conserve the protein's tertiary structure. Given what is known in the art about the likely outcome of substitutions on structure, those in the art

would have likely expected the applicant to have been in possession of a genus of proteins having a tertiary structure similar to SEQ ID NO: 2 although the claim is not so limited. However, conservation of structure is not necessarily a surrogate for conservation of function. In this case, there is no disclosed correlation between structure and function. There is no disclosure of the active site amino acid residues responsible for the catalytic activity. While general knowledge in the art may have allowed one of skill in the art to identify other proteins expected to have the same or similar tertiary structure, in this case there is no general knowledge in the art about similar proteins to SEQ ID NO: 2 to suggest that general similarity of structure confers the activity. Accordingly, one of skill in the art would not accept the disclosure of SEQ ID NO: 2 (or the encoding DNA of SEQ ID NO: 1) as representative of other proteins having sucrose phosphorylase activity. The specification, taken with the pre-existing knowledge in the art of amino acid substitution and the genetic code, fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

12. ***Claim Rejections - 35 USC § 112, first paragraph (Enablement)***

Claims 2-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sucrose phosphorylase sequence of SEQ ID NO: 2, does not reasonably provide enablement for any protein sequence having at least 40% or 60% homology to SEQ ID NO: 2 and which has the biological activity of a sucrose phosphorylase which amounts to a sequence by insertion, deletion or substitution, and having the biological activity of a sucrose phosphorylase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of sucrose phosphorylase broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's

sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequence of SEQ ID NO: 1 and encoded amino acid sequence of dihydrooratase of SEQ ID NO: 1 and the 8 mutants obtained by positional modifications at T47, S62, Y77, V128, K140, Q144, N155 & D249 of SEQ ID NO: 2. Additional modifications of the sequence motif 1 (SEQ ID NO: 25) at positions 14, 29 & 44 are also disclosed.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modification(s) can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of any sucrose phosphorylase by modifying the protein to have a homology of at least 40% or 60% to SEQ ID NO: 2 or a derivative derived from such a sequence by insertion, deletion or substitution, and encoding a protein which has the activity of a heparin synthase, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting sucrose phosphorylase activity; (B) the general tolerance of sucrose phosphorylase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any sucrose phosphorylase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

With regard to claim 4, directed to a sucrose phosphorylase encoded by a polynucleotide sequence that hybridizes to the disclosed sequences, Applicants have not sufficiently defined the stringent conditions (high, medium or low) under which the

hybridizations are to take place. Nucleic acid hybridization assays are extremely sensitive to the conditions in which they are performed, especially the overnight *temperature of 50°C*. The buffer composition, pH, temperature, length of time, salt concentrations, quality and source of template nucleic acid, are all variables which determine the reproducibility of a given hybridization experiment. Given the unpredictability of the art and the nature of hybridization experiments in general, it is not sufficient to merely cite hybridization without a clear and explicit recitation of the conditions associated with the hybridization. For example, the definition of stringency as it pertains to hybridization conditions is subject to interpretation and is different from laboratory to laboratory. Therefore, without a clear and explicit recitation of the conditions which were actually used by Applicants in isolating the claimed polynucleotides which hybridize to the disclosed sequences, the skilled artisan would not be able to practice the claimed invention and would not be reasonably apprised of the metes and bounds of the claimed invention. Without such guidance, the experimentation left to those skilled in the art is undue. Including in the claims the exact nature of the hybridization conditions used to isolate the claimed polynucleotides would aid in overcoming this portion of the rejection.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including dihydrooratase with an enormous number of amino acid modifications of the of SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the numerous sucrose phosphorylase(s) having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

13. Claim 50 is allowed.

14. Claims 1-12, 22-26 are rejected.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached between 8.30 am - 5.00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi can be reached on (571) 272 0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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